Management of Volume Overload in Patients with Heart Failure: The Science and the Art

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The Science and the Art

Figure 3. Percentage increase in RBF index (RBFI) and cardiac index (CI). The percentage increases in RBFI appeared to be greater than those of CI at different doses, reaching statistical significance at 5 μg · kg⁻¹ · min⁻¹.

The ROSE Trial
Dopamine122 vs 61 placebo
We had a very difficult HF patient with recurrent hospitalizations and cardiorenal syndrome. When I was away last week, he was admitted again with renal shutdown that did not respond to diuretics and he was put on dialysis. When I came back, I decided to give it a try and gave him dopamine with amazing response! He gave 1.5 liters on the first day (after giving less than 100ml daily before) and went up to 3 liters a day. He is now off dialysis and off dopamine and everybody think that I'm a king so thank you for your teaching. Ofer Havakuk, MD
The vast majority of acute heart failure episodes are characterized by increasing symptoms and signs of congestion with volume and pressure overload.

The goal of therapy in those patients is the relief of congestion through achieving a state of euvolemia, mainly through the use of diuretic therapy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA pressure</td>
<td>14 mmHg</td>
</tr>
<tr>
<td>Pulmonary wedge pressure</td>
<td>25 mmHg</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>1.9 L/min/m²</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>3.8 L/min</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>1500 dyn x sec/cm²</td>
</tr>
</tbody>
</table>
Volume Overload - Treatment

- Diuretics
- Ultrafiltration
- Renal dose dopamine.
- Vasopressin antagonists.
Patients with volume overload should be treated with IV loop diuretics (1, B).
What is the Dose?
Patients with volume overload

- Initial IV dose greater or equal than the chronic oral daily dose given as either intermittent boluses or continuous infusion (1, B).
Compared with normal subjects, patients with symptomatic HF have 1/4 or 1/3 the natriuretic response to maximally effective doses of loop diuretics. (Vargo DL Clin Pharm Ther 1995).

Figure 1.
Dose–response curve in patients with CHF on chronic loop diuretics.
The DOSE Study

Diuretic Strategies in Patients with Acute Decompensated Heart Failure

G. Michael Felker, M.D., M.H.S., Kerry L. Lee, Ph.D., David A. Bull, M.D., Margaret M. Redfield, M.D., Lynne W. Stevenson, M.D., Steven R. Goldsmith, M.D., Martin M. LeWinter, M.D., Anita Deswal, M.D., M.P.H., Jean L. Rouleau, M.D., Elizabeth O. Ofili, M.D., M.P.H., Kevin J. Anstrom, Ph.D., Adrian F. Hernandez, M.D., Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Abdallah G. Kfoury, M.D., Horng H. Chen, M.B., B.Ch., Michael M. Givertz, M.D., Marc J. Semigran, M.D., Bradley A. Bart, M.D., Alice M. Mascette, M.D., Eugene Braunwald, M.D., and Christopher M. O’Connor, M.D.,
for the NHLBI Heart Failure Clinical Research Network*
DOSE Trial - Design

- **Low-dose:**
  Total daily oral dose.
  (80mg=80mg)

- **High dose:**
  2.5 X total daily oral dose
  (80mg=200mg)
### Low vs. High Dose

Results over 72 hours

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Low dose</th>
<th>High dose</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=151</td>
<td>N=157</td>
<td></td>
</tr>
<tr>
<td>AUC for dyspnea</td>
<td>4478±1550</td>
<td>4668±1496</td>
<td>0.04</td>
</tr>
<tr>
<td>Change in weight (Lb.)</td>
<td>-6.1±9.5</td>
<td>-8.7±8.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Net fluid loss (ml)</td>
<td>3575±2635</td>
<td>4899±3479</td>
<td>0.001</td>
</tr>
<tr>
<td>Chang in NTproBNP (pg/ml)</td>
<td>-1194±4094</td>
<td>-1882±4105</td>
<td>0.06</td>
</tr>
</tbody>
</table>
### Bolus vs. Continuous

Results over 72 hours

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Bolus</th>
<th>Continuous</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC for dyspnea</td>
<td>4456±1448</td>
<td>4699±1573</td>
<td>0.36</td>
</tr>
<tr>
<td>Change in weight (Lb.)</td>
<td>-6.8±7.8</td>
<td>-8.1±10.3</td>
<td>0.20</td>
</tr>
<tr>
<td>Net fluid loss (ml)</td>
<td>4237±3208</td>
<td>4249±3104</td>
<td>0.89</td>
</tr>
<tr>
<td>Change in NTproBNP (pg/ml)</td>
<td>-1316±4364</td>
<td>-1773±3828</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Higher bolus dose 200 mg/d vs 160 mg/d (p=0.06)
Bolus required more frequent dose adjustment
Furosemide in severe CHF: Bolus Injection vs Continuous Infusion
(Dormans et al JACC 1996;28:376-382)
COMPARATIVE EFFECT ON URINE OUTPUT
Ng T, Elkayam U et al  J CV Pharm Therapy  2012

Mean difference b/w baseline and refractory regimen
-48±103*  -109±171*†  -90±90*†
*<0.0001 vs baseline
†<0.0087 between groups

N=160
N=42
N=40

Continuous infusion furosemide
Furosemide + metolazone
Continuous infusion Bumetanide

UO Baseline (mL/h)
UO on Tx (mL/h)
Stepped Pharmacologic Care Algorithm For ADHF

<table>
<thead>
<tr>
<th>Level</th>
<th>Current Daily Furosemide Dose(a), mg</th>
<th>Bolus</th>
<th>Infusion Rate, mg/h</th>
<th>Metolazone (Oral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤80</td>
<td>40</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>81–160</td>
<td>80</td>
<td>10</td>
<td>5 mg daily</td>
</tr>
<tr>
<td>3</td>
<td>161–240</td>
<td>80</td>
<td>20</td>
<td>5 mg twice daily</td>
</tr>
<tr>
<td>4</td>
<td>≥240</td>
<td>80</td>
<td>30</td>
<td>5 mg twice daily</td>
</tr>
</tbody>
</table>

\(a\)Diuretic equivalents: 40 mg furosemide is considered equivalent to 1 mg bumetanide 20 mg torsemide. Adapted from Grodin

Bart BA et al . CARESS Trial NEJM 2012;367:2296-2304
CARESS Trial

B Body Weight

Mean Change from Baseline (lb)

-25
-20
-15
-10
-5
0

24 Hr 48 Hr 72 Hr 96 Hr 7 Days 30 Days 60 Days

P = 0.24
P = 0.33
P = 0.71
P = 0.87
P = 0.97
P = 0.47
P = 0.39
When diuresis is inadequate, it is reasonable to:

- Give high dose of IV loop diuretics (IIa,B) or

- Add a second diuretic (e.g. Thiazide, IIa,B).
Sites and mode of action and effects on sodium reabsorption in the nephron of different diuretics.

European Journal of Heart Failure (2019) 21, 137–155

Acetazolamide
COMPARATIVE EFFECT ON URINE OUTPUT
Ng T, Elkayam U et al  J CV Pharm Therapy  2012

Continuous infusion furosemide
Furosemide + metolazone
Continuous infusion Bumetanide

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N=160
N=42
N=40
## COMPARATIVE EFFECT ON URINE OUTPUT

Ng T, Elkayam U et al : J CV Pharmacol Therap 2012;17:373

<table>
<thead>
<tr>
<th></th>
<th>Continuous infusion</th>
<th>Metolazone</th>
<th>Bumetanide</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence of hyponatremia</strong></td>
<td>29%</td>
<td>43%</td>
<td>63%</td>
<td>0.011 **</td>
</tr>
<tr>
<td><strong>Incidence of hypokalemia</strong></td>
<td>27%</td>
<td>46%</td>
<td>29%</td>
<td>0.095</td>
</tr>
</tbody>
</table>
1,188 ± 476 ml of urine in 12 h during high-dose loop diuretic therapy (IV furosemide: 612 ± 439 mg/day).
## End points at 48 hours

<table>
<thead>
<tr>
<th></th>
<th>Metolazone</th>
<th>Tolvaptan</th>
<th>P value Tolvaptan vs Metolazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net input &amp; output (Liters)</td>
<td>-4.6</td>
<td>-6.43</td>
<td>0.168</td>
</tr>
<tr>
<td>Change in serum Na mEq/L</td>
<td>-1 +/-3</td>
<td>+4 +/-5</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in serum Cl mEq/L</td>
<td>-7 +/-4</td>
<td>+2 +/-3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Change in serum Bicarbonate mEq/L</td>
<td>5 +/-6</td>
<td>+2 +/-4</td>
<td>0.06</td>
</tr>
<tr>
<td>Change in Scr mEq/L</td>
<td>0.3 +/-0.3</td>
<td>+0.03 +/-0.3</td>
<td>0.006</td>
</tr>
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Is there a role for Acetazolamide?

- A meta analysis of 229 patients with HF showed a significant reduction in serum pH, increase in natriuresis, and improvements in apnea.
- ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial ongoing in Europe.
- Effective for the correction of diuretic associated metabolic alkalosis (contraction alkalosis)

Mullens W et al 2018;20:1591-1600
How much volume to remove?
## Volume overload in ADHFrEF

<table>
<thead>
<tr>
<th></th>
<th>Extra Cellular Volume (mL/kg)</th>
<th>Plasma Volume (mL/kg)</th>
<th>Glomerular Filtration (mL/min/1.73/m$^2$)</th>
<th>Renal Plasma Flow (mL/min/1.73 m$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>301 ± 24</td>
<td>58 ± 3</td>
<td>65 ± 8</td>
<td>140 ± 25</td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td>227 ± 13</td>
<td>43 ± 3.0</td>
<td>99 ± 2</td>
<td>479 ± 19</td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>.035</td>
<td>.012</td>
<td>.01</td>
<td>.009</td>
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Extra volume ~ 85 ml/kg or ~ 6.0 L for 70 kg

Serum electrolytes, BUN, Scr should be measured during titration of HF medications including diuretics (Ic).
## Change in Scr and Outcome

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<td>Alive and out of the hospital (days)</td>
<td>50</td>
<td>52</td>
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Increased Scr During Successful Treatment of Volume Overload

What is the Clinical significance?
## Low vs. High Dose

### Results over 72 hours

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CARRESS – HF

Figure 1. Changes in Serum Creatinine and Weight at 96 Hours (Bivariate Response).
# Change in Scr and Outcome

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<td>52</td>
<td>0.42</td>
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Figure 3: Patients’ Global Assessment of Symptoms (VAS) During the 72-h Study Treatment Period and Changes in Serum Creatinine Over Time

(A) Patients’ global assessment of symptoms was quantified as the area under the curve (AUC) of serial assessments from baseline to 72 h. Mean (± SD) AUCs are shown for the group that received a low dose of the diuretic compared with the group that received a high dose. (B) The mean change in serum creatinine level over the course of the study is shown for the group that received a low dose of the diuretic compared with the group that received a high dose. VAS = visual analog scale. Reprinted, with permission, from Felker et al. (18).
CARRESS – HF

**Figure 1.** Changes in Serum Creatinine and Weight at 96 Hours (Bivariate Response).
Figure 2. Changes from Baseline in Serum Creatinine and Body Weight at Various Time Points, According to Treatment Group. The P values were calculated with the use of a Wilcoxon test. The data on creatinine levels reflect results from testing in local laboratories only.
CARRESS - HF

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Mortality and HF hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Mortality Graph" /></td>
<td><img src="image2" alt="Mortality and HF Hospitalization Graph" /></td>
</tr>
</tbody>
</table>

- **Mortality**
  - P-value: 0.465
  - Hazard Ratio: 1.32
  - 95% CI: 0.65, 2.35

- **Mortality and HF Hospitalization**
  - P-value: 0.956
  - Hazard Ratio: 1.31
  - 95% CI: 0.62, 2.84
31% of 903 patients with ADHF developed ≥20% increased GFR (IRF).

IRF was associated with greater incidence of post discharge WRF and increased mortality (HR 1.3, p=0.011)
Effect of IRF vs. WRF on Outcome
Brisco MA et al J Cardiac Failure Oct 2016

- Lower EF (28% v. 38%)
- Lower SBP (129 v. 143)
- More JVD (17% v. 13%)
- More HJR (31% v. 14%)
- Higher BNP (1854 v. 1538)
- Higher BUN (34 v. 26)
- Lower GFR (54 v. 63)
Investigation of association between changes in Scr and 60 d mortality or rehospitalizations.

301 patients in the DOSE trial.

WRF = >0.3 mg/dL increase, IRF = >0.3 mg/dL decrease in Scr.

Increasing Scr was associated with lower risk (HR=0.81, P=.026)

IRF was associated with higher risk (HR 2.52, P<.001).
## Table 2

### Relationship Between Renal Parameters and 6-Month Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Time to Death</th>
<th>Time to Death or Rehospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR*</td>
<td>95% CI</td>
</tr>
<tr>
<td>Baseline SCr</td>
<td>1.20</td>
<td>1.11-1.29</td>
</tr>
<tr>
<td>Baseline eGFR</td>
<td>1.25</td>
<td>1.13-1.38</td>
</tr>
<tr>
<td>Discharge SCr</td>
<td>1.30</td>
<td>1.20-1.41</td>
</tr>
<tr>
<td>Discharge eGFR</td>
<td>1.28</td>
<td>1.14-1.43</td>
</tr>
<tr>
<td>≥0.3 mg/dl ↑ SCr†</td>
<td>1.31</td>
<td>0.81-2.10</td>
</tr>
<tr>
<td>≥25% ↓ eGFR‡</td>
<td>1.49</td>
<td>0.91-2.44</td>
</tr>
</tbody>
</table>

*Among patients with advanced decompensated HF, baseline RI impacts outcomes more than WRF.*
Among patients with advanced decompensated HF, baseline and discharge renal insufficiency impact outcome more than WRF.
WRF in Patients with AHF Undergoing aggressive Diuresis is not associated with Tubular Injury

- Analysis of 283 patients in the ROSE AHF trial.
- WRF = ≥20% decrease in GFR.
- Well validated tubular injury biomarkers N-acetyl-beta-d-glucosaminidase, neutrophil gelatinase-associated lipocalin (NGAL), and kidney injury molecule 1 were measured.

Ahmad T et al
Circulation 2018;137:2016-28
WRF in Patients with AHF Undergoing aggressive Diuresis is not associated with Tubular Injury

- Average dose of furosemide 560- mg /72 hours.
- Urine output 8425 ml.
- WRF occurred in 21%.
- There was no increase in the level of any of the markers of tubular injury.
Is WRF a n ominous prognostic sign inpatients with ADHF?

Metra M et al Circ Heart Fail 2012 ;5:54

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariable HR</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ WRF + CONGESTION</td>
<td>2.44</td>
<td>0.0097</td>
</tr>
<tr>
<td>- WRF + CONGESTION</td>
<td>1.35</td>
<td>0.53</td>
</tr>
<tr>
<td>+ WRF – CONGESTION</td>
<td>1.04</td>
<td>0.88</td>
</tr>
<tr>
<td>- WRF – CONGESTION</td>
<td></td>
<td>Ref</td>
</tr>
</tbody>
</table>

N=599
Relation Between Residual Congestion and Outcome

Post-Discharge Freedom of Congestion Is Associated with Better Prognosis

Survival (%)

- No residual symptoms of congestion (N=80)
- 1-2 residual symptoms of congestion (N=40)
- 3-5 residual symptoms of congestion (N=20)

Survival rates are significantly higher in patients with no or fewer residual symptoms of congestion (p<0.0001).

Symptoms of congestion: orthopnea, jugular venous distention, weight gain ≥2 lbs in a week, need to increase diuretic dose, leg edema

Predischarge BNP and Cumulative Incidence of Death or Re-admission

- Predischarge BNP > 700 ng/l: n=81, events = 38
- Predischarge BNP 350-700 ng/l: n=50, events = 20
- Predischarge BNP < 350 ng/l: n=81, events = 18

Hazard ratios of 15.2 and 5.1 versus 1st BNP range

Prognostic value of residual pulmonary congestion at discharge assessed by lung ultrasound imaging in heart failure. Coiro S et al Eu J Heart Fail 2015;17:1172-1181

Figure 1 Kaplan–Meier survival curves for ≥30 B-lines. Kaplan–Meier survival curves for the combined endpoint (A), heart failure hospitalisation (B), and death (C) in patients with either ≥30 B-lines or <30 B-lines. CI, confidence interval; HR, hazard ratio.
Real World Use of Hypertonic Saline in Refractory Acute Decompensated Heart Failure

150 ml of 3% NaCl to be given over 30 min (300 ml/h), administered simultaneously with high doses of loop diuretic agents.
Take Home Message

- Changes in serum creatinine during the treatment of ADHF should be evaluated in the context of the overall clinical status.
- Keeping in mind that decongestion is the primary goal of treatment.
Many Patients Have Little or No Weight Loss During Hospitalization

Change in weight (lbs)

-20 to -15: 6%
-15 to -10: 13%
-10 to -5: 24%
-5 to 0: 33%
0 to 5: 15%
5 to 10: 3%
>10: 2%

Patients (%)